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Liver transplantation: tacrolimus blood levels variation and survival, rejection and death outcomes

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ABSTRACT – **Background** – Immunosuppressive drugs have important role in transplant of solid grafts, it aim avoid episodes of acute and chronic rejection and improving graft survival and patient survival. In Brazil, in 2016, liver transplantation was the third most frequent, with 1,880 transplants performed, of which 150 in Rio Grande do Sul. Several studies evaluated the association between variability in blood levels of immunosuppressive tacrolimus and late acute cellular graft rejection. **Objective** – To investigate the association of tacrolimus blood levels with clinical outcomes late acute cellular rejection, death, patient survival and graft survival in patients undergoing liver transplantation. **Methods** – This is a retrospective longitudinal study including patients submitted to adult liver transplantation by the Liver Transplantation Group in the *Santa Casa de Misericórdia* Hospital of Porto Alegre, from January 2006 to January 2013, and who used tacrolimus as immunosuppressive therapy. **Results** – Of the 127 patients included in the study, the majority were male (70.1%), 52–60 years old (33.9%) at the transplant. The most frequent causes of liver transplantation in this series were hepatitis C virus and hepatocellular carcinoma (24.4%) and alcohol (15.7%). Thirteen patients had late acute cellular rejection (10.2%); of these, three had two episodes. Regarding severity classification, seven patients had mild late acute cellular rejection. The mean time of rejection after liver transplantation was 14 months (ranging from 8 to 33 months). Overall survival was 8.98 years. Regarding tacrolimus blood levels, 52 patients with a variation ≥2 standard deviations were identified. Of these patients, eight had rejection; however, the association was not significant (P=0.146). A significant association was found between variation ≥2 standard deviations in tacrolimus blood levels and death (P=0.023) and survival (P=0.019). Regarding 5-year follow-up of graft survival, being two standard deviations above increases by 2.26 times the risk of transplanted graft loss, and for each unit of increase of standard deviation of tacrolimus blood levels there is a two-fold increase in the risk of graft loss in 5 years. **Conclusion** – Increased risk of graft loss associated with increased standard deviations of tacrolimus blood levels may indicate the need for more rigorous and prospective monitoring of tacrolimus blood levels.

Keywords – Hepatic transplantation, tacrolimus, transplantation rejection.

INTRODUCTION

Liver transplantation (LT) has made great strides in the last 50 years, with improvements in surgical techniques, patient management and immunosuppressive drugs, making this procedure an effective therapy for patients with liver failure[1,2]. Studies with large databases performed in the United States and Europe showed hepatitis C virus (HCV), alcohol, non-alcoholic steatohepatitis and hepatocellular carcinoma (HCC) as the main causes of liver transplants[3,4].

Considering all indications for liver transplantation during the last 10 years, patient survival at one and 5 years was 85% and 73%, respectively[4]. Data from the Brazilian transplant registry beginning on January 1, 2010 indicate that the survival of patients who underwent liver transplantation and of other grafths at 6 years was 67% and 64%, respectively[5].

Immunosuppressive drugs have significantly contributed to the success of transplants[6]. The expected benefits of immunosuppressive therapy are avoiding episodes of acute and chronic rejection and improving graft survival and patient survival, thus improving quality of life[7]. The most commonly used standard therapies for prophylaxis of hepatic rejection are the calcineurin inhibitors tacrolimus and cyclosporine, combined or not with mycophenolate mofetil or mycophenolate sodium, everolimus, sirolimus and corticosteroid[7-9]. Many immunosuppressants have a narrow therapeutic index and show variable pharmacokinetics. Effective therapy requires individualization of dosage based on therapeutic monitoring of the medication. The greater effectiveness of monitoring depends on knowing the pharmacokinetics of the medication and correlations with clinical outcomes[6]. The adverse effects that can occur with the use of tacrolimus are nephrotoxicity, neurotoxicity, diarrhea and other gastrointestinal disorders, increased risk of infections and malignancies, systemic arterial hypertension, hypercholesterolemia and disorders of glucose metabolism[10,11].

Acute cellular rejection is the most frequent in all types of grafts and its severity is usually measured by grading systems[12]. Some risk factors are associated with late rejection, such as low levels of immunosuppression, autoimmune liver disease and use of interferon[11,13,14]. There is no consensus on the time period of late acute

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cellular rejection, but a systematic review by Nacif et al.[15] defined it as occurring in 3 to 6 months period following transplantation. Retrospective and prospective studies indicate late acute rejection rates of 6.8% to 23%[14-19].

Brazil has today the largest public transplant system in the world, in which about 87% of organ transplants were made with public resources. The National System of Transplants (SNT), created in 1997, offers comprehensive care to the transplanted patient, ranging from organ procurement to patient follow-up[20]. In 2016, 1,880 hepatic transplants were performed in Brazil, of which 150 were performed in Rio Grande do Sul[5]. The South, Southeast and Central West states, and the state of Pernambuco, perform larger numbers of transplants per capita and have larger numbers of transplant teams per capita than the other states of the federation[21]. Transplant centers are concentrated the Southeast and South, where are performed 76% of the LTs in Brazil. Due to its increasing population and inadequate donor organ supply, the country averages 5–10 LTs per million population, far lower than required[22].

This study aims to evaluate the association of the variation in tacrolimus blood levels with the clinical outcomes of late acute cellular rejection, death, patient survival and graft survival in patients undergoing liver transplantation.

METHODS

This is a retrospective, longitudinal study performed with medical records from patients submitted to liver transplantation at the *Irmandade Santa Casa de Misericórdia* de Porto Alegre (ISCMPA) from January 2006 to January 2013. Currently, the ISCMPA is responsible for 60% of the volume of liver transplant surgeries performed in the state of Rio Grande do Sul. The group started liver transplants in 1991 and has since performed more than 1,200 transplants, according to service records.

Included in the study were patients aged older than 18 years of both genders who had their immunosuppressive therapy based on tacrolimus in the 18-month period following liver transplantation and who maintained regular clinical follow-up at the liver transplant outpatient clinic of the ISCMPA, regardless of the diagnosis of liver disease that led to transplantation, comorbidities or other pharmacological treatments. Patients who had only one sample of tacrolimus blood levels were excluded from this analysis because it was not possible to evaluate the blood levels variation. Patients who used cyclosporine or cyclosporine and tacrolimus and patients without record of evaluation of serum tacrolimus levels are excluded from the study.

Data were collected from the medical records and included demographic data (date of birth, gender, race), clinical characteristics such as pre-liver transplant diagnosis and MELD score (Model for Terminal Liver Disease scale used to include the patient in the liver transplant waiting list), date of transplantation, presence of rejection, death, date and cause of death.

MELD is calculated through the results of creatinine, total bilirubin and INR determination and is used to establish the severity of the disease, both in chronic and acute cases. This score began to be used in September 2006; thus, for patients who underwent liver transplantation prior to this period, this information was not available, since there were no results of all the exams necessary to perform the calculation.

The tacrolimus blood levels results from the Central Laboratory of ISCMPA were collected. The methodology used for the test was chemiluminescent microparticle immunoassay (CMIA), with whole blood with EDTA (ethylenediamine tetraacetic acid). Results are reported in ng/mL. Since March 2010, the equipment used is Abbott Architect i2000 SR.

The clinical protocol and therapeutic guidelines immunosuppression in hepatic transplant in adults[7] suggests tacrolimus blood level according to the post-liver transplantation period: 0 to 3 months post-transplantation, 8 to 12 ng/mL; 3 to 6 months, 7 to 10 ng/mL and above 6 months, 5 to 7 ng/mL.

In the first year after liver transplantation, according to guideline, patients should be tested monthly for monitoring immunosuppressant blood levels[7]. Serum tacrolimus levels were considered from the first result after liver transplantation until 18 months after transplantation. The mean exam results were averaged every 30 days, from the date of the transplant to 18 months after the transplant. The intra-patient variation was defined as fluctuation in blood tacrolimus levels in each patient and is represented by the standard deviation.

The first 3 months post-transplantation are the period during which adjustments of tacrolimus blood levels are made in order to find the optimal dose for each patient, so great variations occurs frequently in this period. For this reason, the first 3 months of collection were excluded from mean and variations final analysis. The 3 to 18 month period reflects a time when tacrolimus blood levels were already stabilized.

The variable "late acute cellular rejection" was defined as any acute cellular rejection that occurred after 6 months of transplantation, since rejections that occurred after this period may be associated with immunosuppression. From the initial period up to 6 months after liver transplantation, graft rejection or loss may be caused by factors related to the surgical procedure, in addition to donor-related factors. Biopsies were performed in patients who presented clinical alterations and in laboratory tests suggestive of graft rejection. Late acute cellular rejection was measured, in the follow-up period of 6 months to 5 years after hepatic transplantation, as absent or present rejection, confirmed by liver biopsy. In the case of rejection, were accounted how many rejection episodes were found. In addition, the rejection grade was evaluated according to BANFF criteria[23], such as indeterminate, light, moderate and severe.

Graft loss was defined as a combined outcome variable of death, retransplantation, or patients on the waiting list for retransplantation[24].

The statistics analysis was performed by Student's *t*-test to evaluate the variation of tacrolimus blood levels at the beginning of treatment due to dose adjustment. Associations of the rejection outcome with demographic variables and pre-transplant liver data were analyzed by performing the chi-square test. Normality of continuous variables was confirmed by the Shapiro-Wilk test. Comparison of the outcome with MELD was assessed by Student's *t*-test. Outcomes were assessed using Poisson Regression because of confounding factors. Survival was assessed using the Kaplan-Meier curves and factor comparison using the Log Rank test, as well as Cox regression analysis.

Factors associated with the outcomes of rejection, death and cause of death were evaluated using Poisson regression with robust variance and adjusted for possible confounding variables. The analyses were performed in the SPSS software, version 23, and the statistical significance was 5% (P=value ≤0.05).

This study was approved by the ISCMPA Ethics Committee on November 5, 2015, report number 1.309.979, and CAAE 36507814.1.0000.5335.

RESULTS

From January 2006 to January 2013, 421 transplants were performed, of which 294 were excluded from the present analysis. The exclusion criteria were: use of cyclosporine as immunosuppressant; lack of data on tacrolimus blood levels, death in the initial phase after transplantation; data available only for the first 4 months after transplantation or tests performed in another laboratory.

A sample of 127 patients was included in the study, whose demographic and clinical characteristics pre-liver transplantation can be seen in TABLE 1. The mean MELD score was 24.85 (n=109), with a minimum value of 12 and a maximum of 40. None of the analyzed variables showed an association with graft rejection.

The main diseases that lead to liver transplantation may be combined in many cases, in addition to being associated with HCC. The most frequent combinations of indications for liver transplantation were HCV and HCC (24.4%), HCV, HCC and alcohol (15.7%).

Considering the period after the 6th month from liver transplantation, 107 (84.25%) had no biopsy, 7 (5.51%) performed a biopsy that showed no rejection, and 13 had a biopsy with presence of late acute cellular rejection (10.2%). Of these, 10 (76.9%) had one episode and 3 (23.1%), two episodes. Regarding severity classification, 7 (58.3%) patients had mild acute cellular rejection. The mean time of rejection after hepatic transplantation was 14 months (ranging from 8 to 33 months).

Regarding tacrolimus blood levels, considering the use between the 3rd and 18th month of treatment, 52 patients had a variation greater than two standard deviations; of these patients, eight had rejection; however, the association was not significant (P=0.145), as can be seen in TABLE 2.

Considering that the means of results of tacrolimus blood levels were calculated every 30 days for patients who had a survival of at least 1 year, the mean value found was 7.49 (SD =1.60; P<0.001).

Among the evaluated patients, there were 16 (12.6%) deaths. Regarding graft loss by retransplantation, of the 127 liver transplants five were retransplants, one patient underwent transplantation and retransplantation during the study period, one patient underwent transplantation and, in the follow-up period, hepatic retransplantation due to artery thrombosis, and one patient who underwent a transplant was on the waiting list for retransplantation until March, 2016 due to HCV recurrence. A significant association was found between death and variation greater or equal to two SD in tacrolimus blood levels (P=0.023), as shown in TABLE 3.

The mean overall survival was 8.98 years (8.42–9.54 IC95%) as shown in FIGURE 1. Survival at one, 5 and 6 years was 97%, 86% and 83%, respectively.

TABLE 1. Demographic and clinical characteristics of patients undergoing liver transplantation (ISCMPA, January 2006 – January 2013; n=127).

	Rejection		Total (n=127)	*P* value
	Yes (n=13)	No (n=114)		
Gender				
Male	11 (84.6%)	78 (68.4%)	89 (70.1%)	0.341
Female	2 (15.4%)	36 (31.6%)	38 (29.9%)	
Age at transplantation				
<52 years	7 (53.8%)	35 (30.7%)	42 (33.1%)	
52–60.5 years	2 (15.4%)	41 (36.0%)	43 (33.9%)	0.185
>60.5 years	4 (30.8%)	38 (33.3%)	42 (33.1%)	
Etiology**				
Alcohol	4 (30.8%)	42 (36.8%)	46 (36.2%)	0.768
Hepatitis C virus	10 (76.9%)	70 (61.4%)	80 (63.0%)	0.369
Hepatitis B virus	1 (7.7%)	6 (5.3%)	7 (5.5%)	0.540
Autoimmune hepatitis	1 (7.7%)	4 (3.5%)	5 (3.9%)	0.423
Primary biliary cirrhosis	0 (0.0%)	4 (3.5%)	4 (3.1%)	1.000
Secondary biliary cirrhosis	0 (0.0%)	1 (0.9%)	1 (0.8%)	1.000
Cryptogenic cirrhosis	1 (7.7%)	0 (0.0%)	1 (0.8%)	0.102
Hemochromatosis	0 (0.0%)	2 (1.8%)	2 (1.6%)	1.000
NASH*	0 (0.0%)	3 (2.6%)	3 (2.4%)	1.000
Polycystic disease	0 (0.0%)	2 (1.8%)	2 (1.6%)	1.000
Budd Chiari	0 (0.0%)	1 (0.9%)	1 (0.8%)	1.000
Oxalosis	0 (0.0%)	2 (1.8%)	2 (1.6%)	1.000
Carcinoid tumor	0 (0.0%)	1 (0.9%)	1 (0.8%)	1.000
Hepatocellular carcinoma**	7 (53.8%)	63 (55.3%)	70 (55.1%)	1.000
Age of donor (n=124)				
≤41 years	2 (16.7%)	40 (35.7%)	42 (33.9%)	
41–54 years	4 (33.3%)	39 (34.8%)	43 (34.7%)	0.27
>54 years	6 (50.0%)	33 (29.5%)	39 (31.5%)	

*NASH: nonalcoholic steatohepatitis. **Information is presented individually, in most cases there is a combination of etiologies and association with hepatocellular carcinoma, and this is why there are more cases than the sample of 127. Chi-square test (significance *P* value ≤0.05).

TABLE 2. Variation of tacrolimus blood levels and use of mycophenolate associated in patients undergoing liver transplantation in relation of acute late graft rejection (ISCMPA, January 2006 – January 2013; n=127).

	Rejection		Gross OR (CI95%)	*P*-value	Adjusted OR* (CI95%)	*P* value
	Yes (n=13)	No (n=114)				
Serum levels variation						
<2 SD	5 (6.7%)	70 (93.3%)	1		1	
≥2 SD	8 (15.4%)	44 (84.6%)	2.31 (0.80–6.66)	0.122	3.05 (0.68–13.62)	0.145
Use of mycophenolate						
No	7 (9.7%)	82 (92.1%)	1		1	
Yes	6 (15.8%)	32 (84.2%)	2.01 (0.72–5.58)	0.180	1.64 (0.35–7.64)	0.526

*Poisson regression: adjusted for age at liver transplantation, donor age, gender and MELD= Model for End-Stage Liver Disease. SD: standard deviation; OR: odds ratio; CI: confidence interval.

TABLE 3. Outcomes in association with standard deviation of mean tacrolimus blood levels (ISCMPA, January 2006 – January 2013; n=127).

Outcome	<2 SD	≥2 SD	CI95%	*P* value
Death	5 (6.7%)	11 (21.2%)	3.17 (1.17–8.59)	0.023
Not specified cause	3 (4.0%)	3 (5.8%)	1.44 (0.30–6.87)	0.646
Sepsis	2 (2.7%)	4 (7.7%)	2.89 (0.55–15.17)	0.211
Hepatocellular carcinoma	0 (0.0%)	2 (3.8%)	–	
Multiple organ failure	0 (0.0%)	1 (1.9%)	–	–
Pulmonary carcinoma	0 (0.0%)	1 (1.9%)	–	–
Rejection				
Mild acute cellular	3 (60%)	55 (62.5%)	0.94 (0.23–3.79)	0.928
Moderate acute cellular	2 (40%)	3 (37.5%)	0.40 (0.14–1.17)	0.094
Number of episodes	1.20 (±0.447)	1.25 (±0.463)		0.851

SD: standard deviation; Poisson Regression.

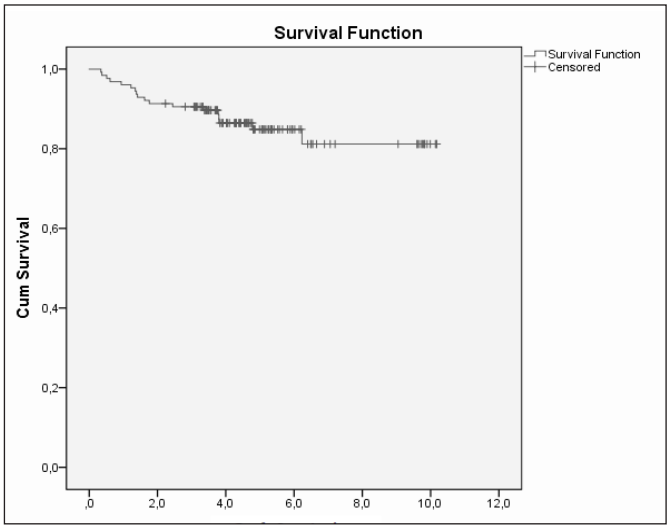

FIGURE 1. Overall survival of liver transplant recipients who underwent immunosuppressive therapy based on tacrolimus levels (ISCMPA, January 2006 – January 2013; n=127).

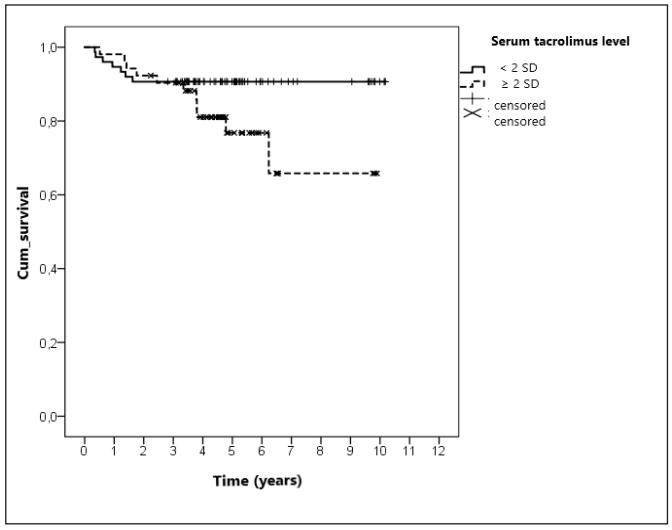

FIGURE 2. Survival of patients who underwent liver transplantation in association with standard deviation of tacrolimus blood levels (ISCMPA, January 2006 – January 2013; n=127).

FIGURE 2 shows a non-significant association between patient survival and variation in standard deviation of tacrolimus blood levels (*P*=0.079). The mean survival was 9.31 years (CI95% 8.70–9.92) for patients who show variation from to two SD and 7.89 years (CI95% 6.79–8.99) for patients with a variation in tacrolimus blood levels greater than two SD.

In relation to the 5-year follow-up of graft survival, being two SD above the mean tacrolimus blood level increases by 2.26 times the risk of loss of the transplanted graft in relation to those below two SD (CI95% 0.66–7.80; *P*=0.196), as shown in FIGURE 3.

For each unit of increase of SD of tacrolimus blood levels, there is a twofold increase in the risk of loss of the transplanted graft at 5 years (CI95% 1.17–3.48; *P*=0.012).

DISCUSSION

Among the causes of liver transplantation, HCV was present in 63% of the cases. The South region accounts for 31.5% of HCV cases reported in the country in 2019. The age group with more HCV cases reported in Brazil, including both genders, is 55 to 59 years old (57.6%). Men account 57.6% of diagnosed cases[25]. In a study conducted in Rio Grande do Sul from 2010 to 2011, the majority of reported cases of HCV occurred in the white male population in

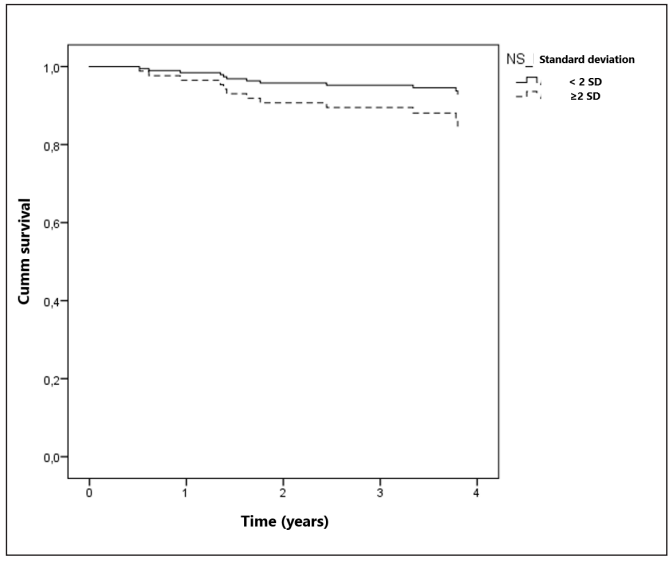

FIGURE 3. Graft survival of liver transplants in association with standard deviation of tacrolimus blood levels (ISCMPA, January 2006 – January 2013; n=127).

the age group between 30 and 49 years[26]. These data reinforce the results regarding gender and age, since the evolution to cirrhosis can take about 20 years from the initial contact with the virus[27].

The causes of transplantation found in the present study are similar to the worldwide data, in which HCV and alcohol are pointed as the main causes[3,4]. The late graft rejection rate found in this study was 10.2%, similar to other studies, in which the rates ranged from 6.8 to 23%[14,15,18,19,28,29].

The standard deviation of tacrolimus blood levels was significantly associated with survival (P=0.019) and death (P=0.023). Studies have found an association between standard deviation of tacrolimus blood levels and late graft rejection[30-33]. Studies comparing high and low variability of tacrolimus blood levels in renal transplant recipients found a significant difference in graft survival (P=0.0004 and P=0.003); however, this did not occur in a study that evaluated patient survival (P=0.116)[28-30]. A study in Canada with 144 adult patients submitted to solid organ transplantation found that an increase in standard deviation greater than two was associated with an increased risk of graft loss in all groups of different transplanted organs[30]. Studies in children suggest that variation in tacrolimus blood levels was a predictor of rejection and appears to be very promising for early identification of rejection risk in children[31-33].

In the present study, there was a two-fold increase in the risk of graft loss (CI95% 1.17–3.48; P=0.012) per each unit of increase of standard deviation of tacrolimus blood levels. Studies found that an increase of one unit in the standard deviation of tacrolimus blood levels, increases the risk of graft loss by 3.49 (CI95% 1.31–9.29; P=0.012), 1.6 (CI95% 1.2–2.0; P=0.003) and 1.005 (P=0.04)[30,33,34].

After liver transplantation, the use of immunosuppressive drugs becomes a challenge, since a very high or very low dosage may be detrimental to the treatment. Patients who develop sepsis after transplantation often have an empirically reduced immunosuppression. On the other hand, patients who present rejection are treated with increasing doses of the drugs. The purpose of monitoring is to optimize immunosuppression before the occurrence of undesirable clinical events[8]. Immunosuppressive therapy should be tailored to each patient, balancing the risks of rejection and over immunosupression[35].

A prospective and randomized study concluded that the implementation of pharmaceutical care presented positive results, being easily integrated into the daily routine. Patients who received pharmaceutical care combined with routine clinical care showed a significant improvement in compliance with immunosuppressive therapy. The participation of the clinical pharmacist in the care of post-transplant patients is intended to optimize therapy and improve adherence to medications[36].

In addition, it is necessary to recognize and control the factors that contribute to the variation of blood levels of immunosuppressive drugs. These factors include standards of medical practice, new medicines, new diseases, drug-drug and drug-food interactions, patient metabolism, genetic factors, diarrhea, non-compliance with treatment, and type of tacrolimus dosing method[33,37].

In the present study, 3 (2.4%) retransplants were performed, one for primary biliary cirrhosis, one for HCV recurrence and another for hepatic artery thrombosis. In a study carried out in Europe, considering the period from May 1968 to December 2009, with 93,634 hepatic transplants, it was found that retransplantation was indicated in 5,596 (7%) cases, most of them due to technical (37%), vascular (27%) and biliary (10%) complications, primary non-functioning (25%) and rejection (19%, with chronic rejection being 14%). Recurrence of the primary disease, mostly non-tumoral, occurred only in 11% of the cases[4].

The overall mortality found in this study was 12.6% and the main cause of death was sepsis (38.9%). In a study carried out in Europe, the mortality rate was 23%, considering 18,186 patients with liver transplantation or retransplantation. The general causes of death were multiple organ failure and cerebrovascular, cardiovascular, pulmonary and renal complications (29%); recurrence of primary disease (20%, with 11% due to cancer); sepsis (18%, with 9% due to bacterial infection); technical complications (5%, 3% due to bleeding and vascular complications) and rejection (4%, with 3% due to chronic rejection). When only patients who survived more than 6 months are considered, there are fewer technical complications, infection and general complications, and an increase in tumor and non-tumor recurrence, new tumor and rejection. Data from the last 10 years of the study showed an overall mortality rate of 16% with the same distribution of causes of death observed in the population since 1988[4].

Among the limitations of the present study, we can mention the retrospective design. In addition, the average tacrolimus blood collection during the 12-month period after liver transplantation was 7.49, that is, at least one collection was not performed every 30 days of follow-up and the lack of this data may influence the results. Asymptomatic transplant patients without laboratory alterations did not undergo biopsy, and there may be among these cases of acute cellular graft rejection. Biopsy is an invasive procedure, not indicated without need justified by clinical evaluation. However, the data demonstrated the variation in tacrolimus blood levels and point to the importance of monitoring and its implication in clinical outcomes.

The findings on rejection, survival and death may have been influenced by other factors. However, increased risk of graft loss associated with increased standard deviations of tacrolimus blood levels may indicate the need for more rigorous monitoring of tacrolimus blood levels.

This was a retrospective study and we believe it opens the door to a prospective study where patients are evaluated from the post-transplant period, assessing serum tacrolimus levels and outcomes, not just rejection. In addition, a prospective study also makes it possible to assess other factors related to the outcomes. Prospective studies with the inclusion of patient follow-up by pharmacist, added to the health team, could be performed to improve treatment adherence and variation in tacrolimus blood levels in patients who underwent liver transplantation.

Intra-patient monitoring of tacrolimus blood levels by standard deviation is an inexpensive method that can be incorporated into the clinical follow-up of patients with liver transplantation.

Routine monitoring of tacrolimus blood levels should be used in conjunction with the clinical evaluation of the patient in order to optimize immunosuppressive therapy. Through integrated multidisciplinary team action it is possible to increase the quality of care and decrease the chances of undesirable outcomes.

CONCLUSION

The results of this study show that variations in tacrolimus serum levels greater than two standard deviations are associated with survival and death. The early identification of patients with varying blood levels of tacrolimus with the accurate monitor-

ing of the drug blood levels may be important in the follow-up of patients who undergo liver transplantation and can prevent unfavorable outcomes.

Authors' contribution

Maciel NB: study concept and design, acquisition of data, data interpretation, manuscript preparation. Schwambach KH: manuscript preparation, critical revisions. Blatt CR: study concept and design, manuscript preparation, critical revisions.

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RESUMO – Contexto – Os imunossupressores desempenham importante papel no transplante de órgãos sólidos, com o objetivo de evitar a rejeição aguda e crônica, aumentando o tempo de sobrevida do órgão e do paciente. No Brasil, em 2016, o transplante de fígado foi o 3° mais frequente, com um número de 1.880 transplantes, sendo 150 realizados no Rio Grande do Sul. **Objetivo** – Investigar a associação da variação dos níveis sanguíneos de tacrolimo com os desfechos clínicos, rejeição celular aguda tardia, óbito, sobrevida de paciente e enxerto em pacientes submetidos ao transplante hepático. **Métodos** – Trata-se de um estudo longitudinal retrospectivo, no qual foram incluídos os pacientes submetidos ao transplante hepático adulto pelo grupo de transplante hepático na Irmandade Santa Casa de Misericórdia de Porto Alegre, no período de janeiro de 2006 a janeiro de 2013, e que fizeram o uso de tacrolimo como terapia imunossupressora. **Resultados** – Dos 127 pacientes incluídos no estudo, a maioria era do gênero masculino (70,1%), caucasiana (86,4%), com idade entre 52 e 60 anos (33,9%). As associações de causas mais frequentes para transplante hepático foram vírus da hepatite C, carcinoma hepatocelular (24,4%) e álcool (15,7%). Um total de treze pacientes apresentaram rejeição celular aguda tardia (10,2%); destes, três tiveram dois episódios. O tempo médio de rejeição após o transplante hepático foi de 14 meses, variando de 8 a 33 meses. A sobrevida global foi de 8,98 anos. Em relação aos níveis sanguíneos de tacrolimo, foram identificados 52 pacientes com uma variação maior ou igual a dois desvios-padrão. Destes pacientes, oito tiveram rejeição, contudo, a associação não foi significativa (P=0,146). Foi encontrada uma associação significativa entre a variação maior ou igual a dois desvios-padrão nos níveis sanguíneos de tacrolimo com óbito (P=0,023) e sobrevida (P=0,019). Em relação ao acompanhamento de sobrevida do enxerto em cinco anos, estar dois desvios-padrão acima aumenta em 2,26 vezes o risco de perda do enxerto transplantado, e a cada unidade de aumento de desvio-padrão dos níveis sanguíneos de tacrolimo há um aumento de duas vezes no risco de perda do enxerto transplantado em 5 anos. **Conclusão** – O aumento do risco da perda do enxerto associado ao aumento da variação dos níveis sanguíneos de tacrolimo pode indicar a necessidade do acompanhamento mais rigoroso e prospectivo dos níveis sanguíneos de tacrolimo.

Palavras-chave – Transplante hepático; tacrolimo; rejeição de transplante.

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